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'Chronic duodenitis': A clinical pathological entity?

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EDITORIAL SYNOPSIS This is the first reported study correlating clinical, radiological, secretory, and histological data in dyspeptic patients. Patients with normal radiographs but complaining of ulcer symptoms showed similar inflammatory changes in the duodenum as did patients with duodenal ulcers with normal levels of acid secretion. These studies add support to the concept of a definite clinical physiopathological entity, 'chronic duodenitis', but only follow-up studies will show whether or not these are early cases of duodenal ulcer.

There is a large group of patients who complain of gastrointestinal symptoms but in whom radiological and endoscopic studies are normal. These patients, because of the lack of evidence of organic gastrointestinal disease, are frequently labelled by clinicians with the diagnosis of 'functional dyspepsia'. Out of this rather heterogenous group of patients with multiple complaints, a more distinct group can be separated on the basis of a careful clinical history. They present with periodic gnawing epigastric hunger pains relieved by food and alkali. These symptoms mimic those of duodenal ulcer to such an extent that a differentiation is impossible, except that radiologically they present a duodenal cap without the slightest evidence of deformity, scar, or 'irritability'. On the basis of this typical ulcer history, patients in this group are distinct from others whose symptoms include belching, post-prandial distension, nausea, vomiting, crampy abdominal pains, irregularities of bowel function, and other indeterminate 'atypical' complaints.

It was of interest to investigate whether patients with typical duodenal ulcer complaints but without radiological evidence of such might have some type of non-ulcerating duodenal disease. If so, does their duodenal histology or gastric secretory function differ from that of patients with functional dyspepsia but atypical symptoms, on the one hand, or from patients with actual duodenal ulcer, on the other? To answer these questions, four distinct groups of individuals were chosen for study: 1, normal controls; 2, patients with 'atypical' gastrointestinal symptoms and negative radiographs; 3, patients with a typical ulcer history but with negative radiographs; and, 4, patients with typical ulcers, proved by their history and radiographs. The present communication reports a clinical, radiological, histopathological, and gastric secretory study on these four groups.

MATERIALS AND METHODS

SUBJECTS Group 1 consisted of normal volunteers without history or radiological evidence of upper gastrointestinal disease: 10 university students between the ages of 21 and 31 years (average 24 years), of whom two were female and eight male.

Group 2 consisted of six patients with atypical upper gastrointestinal symptoms, consisting of post-prandial abdominal distension, nausea, crampy pains, and belching. They had no radiological signs of peptic ulcer, gall bladder or colonic disease. Their ages varied between 35 and 50 years (average 43 years). There were five females and one male.

Group 3 consisted of 21 patients with typical symptoms of duodenal ulcer, but without radiological evidence of upper gastrointestinal disease. Their ages varied between 20 and 56 years (average 33 years). There were seven females and 14 males.

Group 4 consisted of 36 patients with radiological evidence of duodenal ulcer disease. All 36 were symptomatic and therefore their ulcer was considered to be active at the time of the study. In 31 an ulcer crater could be demonstrated, while in five there was so much deformity of the duodenal cap that a definite crater could not be demonstrated. Their ages varied between 21 and 58 years (average 37 years). There were 12 females and 21 males.

All cases were classified on the basis of clinical and radiological findings into its appropriate group. This classification was considered final and served as the basis

of the study. Following this, secretory study was undertaken and a biopsy specimen obtained. No patient was moved from his originally designated group whatever the result of the biopsy or secretory study.

STUDIES Each of the subjects had an upper gastrointestinal radiological study, a maximum histamine stimulation test, and a duodenal biopsy. The maximum histamine stimulation test was performed according to the description of Kay (1953). The results were expressed in milliequivalents hydrochloric acid secreted in 45 minutes under basal conditions and in milliequivalents hydrochloric acid secreted between 15 and 45 minutes after the injection of 0·04 mg. histamine base per kilogram body weight. Biopsies were obtained from the duodenal cap using the Carey capsule (Carey, 1964). The capsule was allowed to pass until it reached the upper jejunum. Its position was confirmed in the jejunum by fluoroscopic examination and then under fluoroscopic control, gradually withdrawn into the duodenal cap. On withdrawal a typical pattern of direction could be observed as the capsule passed from the jejunum through the different portions of the duodenum until it reached the cap (Beck, Connor, and Lacerte, 1965).

HISTOPATHOLOGY After removal from the instrument, the duodenal biopsies were laid flat with the mucosal surface up, as described by Rubin, Brandborg, Phelps, and Taylor (1960) and fixed in formalin. They were separately embedded in paraffin in such a manner that the microscopic sections were cut at right angles to the mucosal surface. The sections were stained with haematoxylin and eosin.

The biopsies were graded from grades 0 to 4 (see below) on two separate occasions by the same observer, without his having any knowledge of which clinical group the patients belonged to.

The grading of the duodenal biopsies took into account all features of the microscopic structure; however, from a practical point of view, only a few features were pertinent. Most significant was the amount of infiltration by chronic inflammatory cells, lymphocytes, plasma cells, and mast cells. Second, but much less significant, was the amount of oedema and vascularity in the lamina propria. A third feature of note was mucus secretory cell replacement of the normal duodenal epithelium, and last and rarely found was thickening of the mucosa with flattening of the villi. Grade 0 had perfectly normal structure with no infiltrate (in this study of 86 biopsies only one biopsy was so graded and at one reading only). Grade 1 exhibited a very mild infiltrate (Fig. 1), grade 2 a moderate sprinkling of round cells in the lamina propria (Fig. 2), grade 3, moderately heavy inflammatory cell infiltration with some increased vascularity (Fig. 3); grade 4, a heavy diffuse inflammatory cell infiltration (Fig. 4), plus in some biopsies the other features mentioned above (Figs. 5 and 6).

The interpretation of the grade was of necessity a subjective one. In a few cases it was impossible categorically to differentiate between two full grades and these were then graded as half values; for example, if the difficulty was between grades 2 and 3, the biopsy was graded as 2½.

All the biopsies were read on two different occasions by the same examiner who, on the second occasion, had no knowledge of the previous grading. In the majority of cases there was excellent agreement between the two readings. If there was a discrepancy between the two, for statistical calculations the mean of the two readings was taken as the final result, *i.e.*, if on the first reading the specimen was marked 2½ and on the second reading the grading was 2, the final grading was considered to be 2·25. This latter figure was then included in the statistical calculations.

RESULTS

The results are shown in Figure 7. The upper columns show the results of the secretory studies while the scattergrams below demonstrate the final pathological gradings.

Table I shows the two separate readings of the duodenal biopsies and their averages for each patient.

GROUP 1: NORMAL CONTROLS The maximum histamine stimulation tests were within the normal limits as described by Kay (1953) (mean and S.D.: basal secretion 2·5 ± 1·43 mEq. HCl: after maximum histamine stimulation 10·2 ± 1·86 mEq. HCl). Duodenal biopsy gradings were never higher than 2½.

GROUP 2: FUNCTIONAL DYSPEPSIA WITH ATYPICAL SYMPTOMS Secretory studies revealed a mean and S.D. of 0·9 ± 0·44 mEq. HCl. in the basal secretions and a mean and S.D. of 11·0 ± 2·44 after maximum histamine stimulation.

Duodenal biopsy gradings were all below 2½.

GROUP 3: PATIENTS WITH TYPICAL SYMPTOMS OF DUODENAL ULCER WITH NORMAL RADIOGRAPHS The mean and S.D. of basal secretions was 1·5 ± 1·56 mEq.HCl. After maximum histamine stimulation this rose to 8·1 ± 4·16 mEq. HCl secreted. Thus the basal and maximal histamine-stimulated secretions fell within the normal range in almost all these patients. One case showed absolute achlorhydria on two separate occasions. Only two cases showed raised acid secretions and both of these were only moderate. Duodenal biopsy gradings were in the majority grade 3 or 4. Only five of the 21 had biopsy grading in the same range as the upper limit found in the controls.

GROUP 4: DUODENAL ULCER Although the basal secretion was significantly raised, this rise was only moderate as compared to the normals (mean and S.D. 4·1 ± 2·63 mEq. HCl secreted). The maximum histamine stimulation response was significantly increased in 31 of the 36 patients (mean and S.D. 16·9 ± 6·51 mEq. HCl secreted). Duodenal biopsy

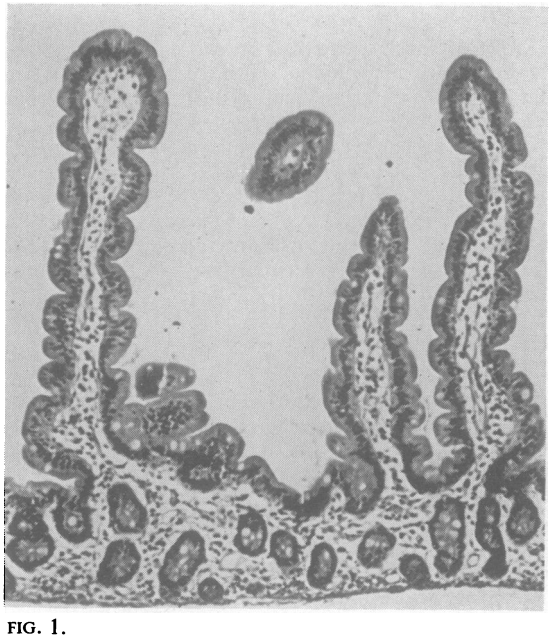

FIG. 1.

FIG. 1. *Photomicrograph of a duodenal biopsy showing grade 1 features. The villous pattern of the mucosa is well maintained. There is only a sprinkling of round cells in the lamina propria. Haematoxylin and eosin* × *100.*

FIG. 2. *Photomicrograph showing grade 2 features with a slightly heavier infiltration in the lamina propria. Haematoxylin and eosin* × *125.*

FIG. 3. *Photomicrograph showing grade 3 features. The infiltrate in the lamina propria is moderately heavy. Haematoxylin and eosin* × *125.*

FIG. 4. *Photomicrograph showing grade 4 features. The infiltrate is very marked and the villi are blunted and swollen. Haematoxylin and eosin* × *125.*

FIG. 5. *Similar to Fig. 4 and showing a lymphoid follicle. Haematoxylin and eosin* × *125.*

FIG. 6. *Higher-power view of a grade 4 biopsy to show mucous cell replacement of the surface epithelium and the plasma cells and lymphocytes that make up the lamina propria infiltrate. Haematoxylin and eosin* × *400.*

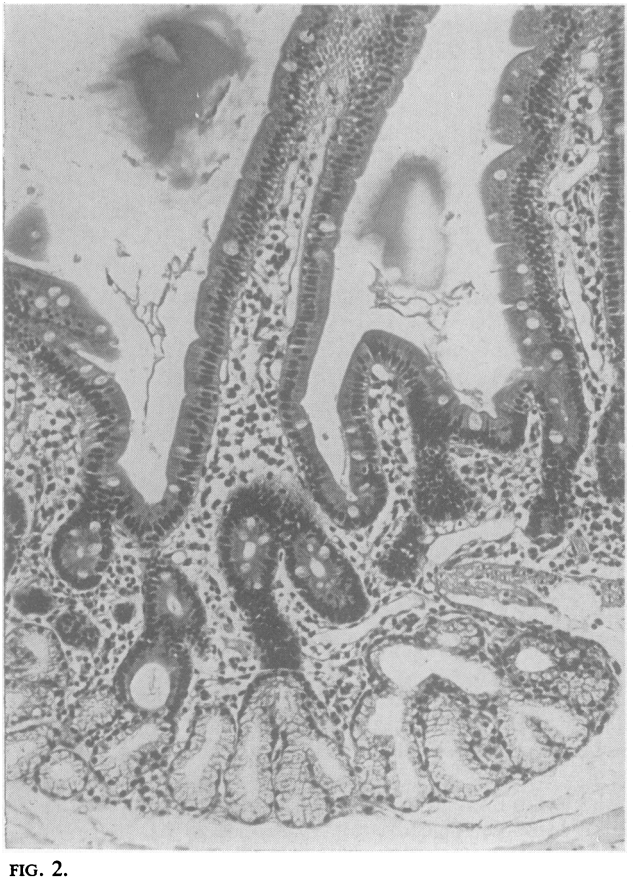

FIG. 2.

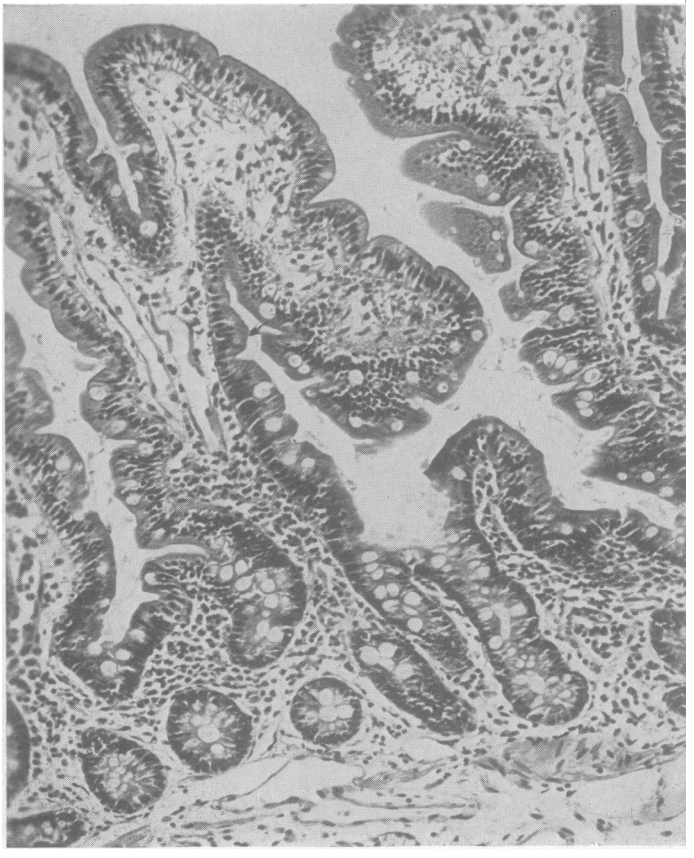

FIG. 3.

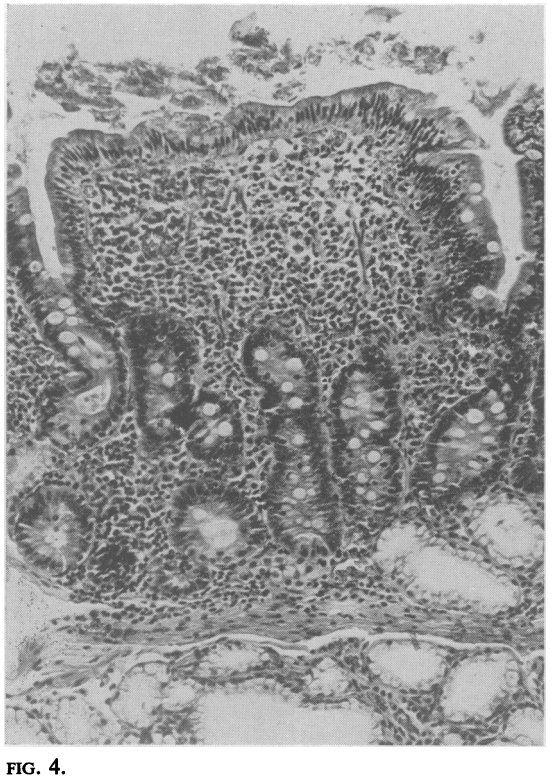

FIG. 4.

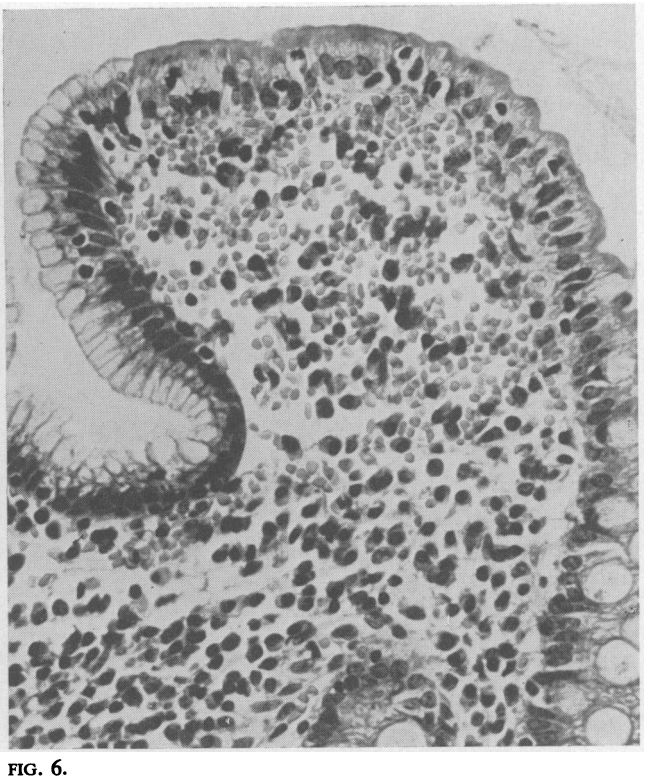

FIG. 6.

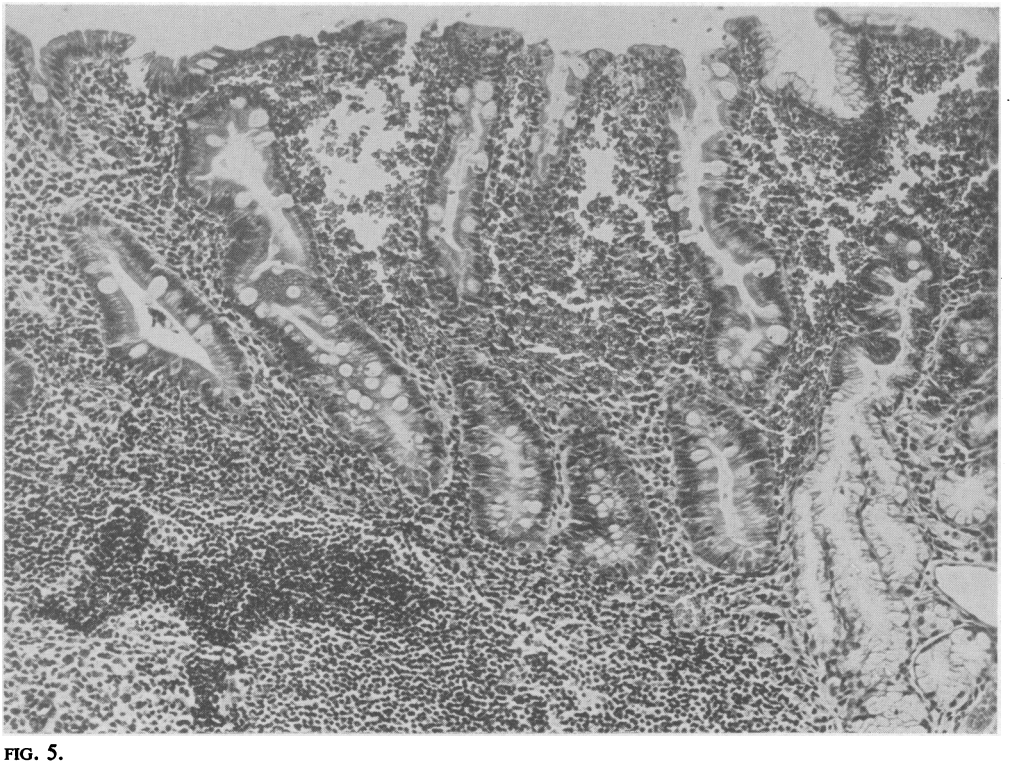

FIG. 5.

TABLE I

DUPLICATE PATHOLOGICAL GRADINGS

Group 1: Normal Controls				*Group 2: Functional Dyspepsia*				*Group 3: Duodenitis*				*Group 4: Duodenal Ulcer*			
Case No. and Sex	*First Reading*	*Second Reading*	*Mean No.*	*Case No. and Sex*	*First Reading*	*Second Reading*	*Mean*	*Case No. and Sex*	*First Reading*	*Second Reading*	*Mean*	*Case No. and Sex*	*First Reading*	*Second Reading*	*Mean*
1 M	2	—	2·0	1 F	2	2½	2·25	1 F	3	3	3·0	1 F	2½	3	2·75
2 M	2	3	2·5	2 F	2	—	2·0	2 M	3½	3	3·25	2 M	4	3	3·5
3 M	2	3	2·5	3 F	2½	2	2·25	3 M	2½	3	2·75	3 F	2	2½	2·25
4 M	1½	1	1·25	4 M	2	2	2·0	4 M	4	4	4·0	4 F	4	4	4·0
5 M	2	1	1·5	5 F	2	2	2·0	5 M	3	3	3·0	5 F	3	3	3·0
6 M	0	1	0·5	6 F	2	2	2·0	6 M	2½	2	2·25	6 F	3	4	3·5
7 M	2	3	2·5	Mean			2·1	7 M	3	3	3·0	7 M	4	4	4·0
8 F	2	3	2·5	S.D.			±0·12	8 F	2	3	2·5	8 F	4	4	4·0
9 F	1	2	1·5					9 M	1	1	1·0	9 F	1	1	1·0
10 M	½	2	1·25					10 M	4	4	4·0	10 M	3	3	3·0
Mean			1·8					11 F	3	3	3·0	11 F	4	4	4·0
S.D.			±0·70					12 F	3	3	3·0	12 M	3	3	3·0
								13 M	2½	3	2·75	13 F	4	4	4·0
								14 M	3	3	3·0	14 F	4	4	4·0
								15 F	3	3	3·0	15 M	3	2	2·5
								16 M	4	4	4·0	16 M	4	4	4·0
								17 M	3	2	2·5	17 M	3	1	2·0
								18 M	3	4	3·5	18 M	4	4	4·0
								19 M	4	4	4·0	19 F	2	2½	2·25
								20 F	3	2	2·5	20 M	4	4	4·0
								21 F	4	4	4·0	21 M	4	4	4·0
								Mean			3·1	22 M	3	3	3·0
								S.D.			±0·45	23 M	3	3½	3·25
												24 M	3	3½	3·25
												25 M	4	4	4·0
												26 M	3	3½	3·25
												27 F	3	3	3·0
												28 M	3	4	3·5
												29 M	—	2½	2·5
												30 M	3	3	3·0
												31 M	3	2½	2·75
												32 M	4	4	4·0
												33 F	2	2	2·0
												34 M	3	4	3·5
												35 M	3½	3	3·25
												36 M	2½	3	2·75
												Mean			3·2
												S.D.			±0·62

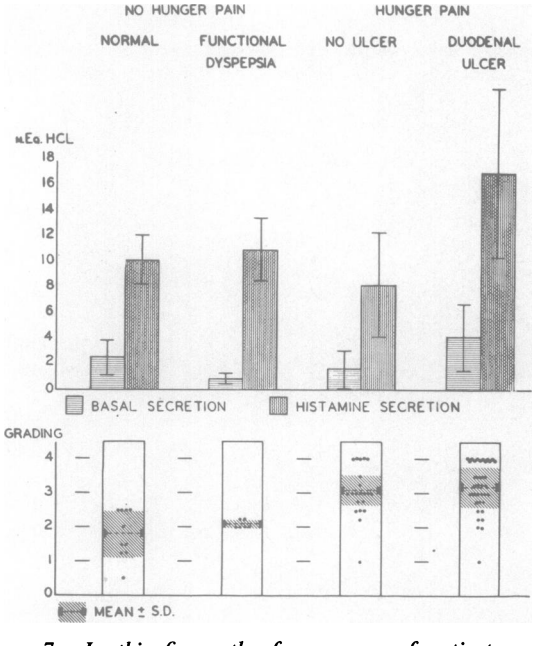

FIG. 7. *In this figure the four groups of patients are designated on the top. Both the upper columns representing the mean and ± S.D. of secretions, as well as the scattergrams in the lower half of the figure representing duodenal pathology, correspond to the groups designated on the top.*

gradings were, in the majority, grade 3 or 4. Only seven of the 36 cases fell into a grade comparable to the control series.

In a negative sense it may be of interest to mention that in none of the 36 biopsies from patients with radiologically proven duodenal ulcer and high acid secretion, nor in the 21 biopsies of group 3 did we find either intravascular thrombi, arteritis, intimal arteriolar thickening, or coagulation necrosis of the superficial part of the mucosa.

STATISTICAL ANALYSIS

The critical problem in this study is the reproducibility of the pathological grading. Although it is conceivable that readings may differ from pathologist to pathologist, the validity of this study depends on the reproducibility of the relative gradings from specimen to specimen. It is for this reason that each specimen was scrutinized on two occasions. The error of the method was calculated from the

differences of the two readings. Table II demonstrates the result of these calculations. The relatively high error in grade 0-1 is due to the fact that only one specimen was ever graded as 0 and only seven as 1. This small number of specimens naturally results in exaggeration of the calculated error. In all other gradings and in the overall total the error is small (15%).

TABLE II

ERROR OF THE METHOD OF DUPLICATE GRADING

Grading	*Mean of Differences*	± *S.D.*	± *S.E.*	*Percentage Error*
0-1[1]	0·88	0·65	0·23	26
1-2[2]	0·70	0·43	0·10	14
2-3[3]	0·53	0·48	0·07	13
3-4[4]	0·37	0·47	0·06	16
All gradings	0·40	0·47	0·06	15

[1]All cases including a grading 0 or 1
[2]All cases including a grading 1 or 2
[3]All cases including a grading 2 or 3
[4]All cases including a grading 3 or 4

Statistical analysis of the secretory activity reveals that the basal secretion of group 2 (atypical symptoms) is lower ($p < 0{\cdot}01 > 0{\cdot}001$) and of group 4 (duodenal ulcer) is higher than the normal (Table III). The group with hunger pains but no ulcer puts out basal secretions similar to those of the normals.

TABLE III

BASAL SECRETION

Significance of Differences between	*Group 2*	*Group 3*	*Group 4*
Group 1	$p < 0{\cdot}01 > 0{\cdot}001$	Not significant	$p = 0{\cdot}02$
Group 2		Not significant	$p < 0{\cdot}001$
Group 3			$p < 0{\cdot}001$

Histamine-stimulated secretion of the duodenal ulcer group is higher ($p < 0{\cdot}001$) than that of the normals, but there is no difference between groups 1, 2, and 3 (Table IV).

TABLE IV

HISTAMINE-STIMULATED SECRETION

Significance of Differences between	*Group 2*	*Group 3*	*Group 4*
Group 1	Not significant	Not significant	$p < 0{\cdot}001$
Group 2		$p = 0{\cdot}05$	$p = 0{\cdot}05$
Group 3			$p < 0{\cdot}001$

Table V demonstrates that the duodenal biopsies of normal subjects and of patients with atypical symptoms are similar. These differ significantly from those of patients of groups 3 and those with proven duodenal ulcer, group 4. The biopsies of patients with a history of ulcer but without radiological evidence of ulcer do not differ from those obtained from patients with ulcer disease.

TABLE V

GRADINGS OF DUODENAL BIOPSIES

Significance of Differences between	*Group 2*	*Group 3*	*Group 4*
Group 1	Not significant	$p < 0{\cdot}001$	$p < 0{\cdot}001$
Group 2		$p < 0{\cdot}001$	$p < 0{\cdot}001$
Group 3			Not significant

DISCUSSION

The first biopsy study of the duodenum dates back to 1956 and 1957 (Shiner, 1956; Shiner, 1957; Doniach and Shiner, 1957), but only a few subsequent reports have appeared (Mahlo, 1960; Cheli, Dodere, and Celle, 1961a and b; Aronson and Norfleet, 1962). In the main they are at variance with the present study in that they concerned themselves mostly with the differences in the duodenal histology between patients with radiologically negative dyspepsia (irrespective of the type of symptoms) and those with duodenal ulcer. They neither correlated their findings with secretory studies not differentiated clearly between the radiologically negative dyspepsia with atypical symptoms and the group with typical hunger-type ulcer pain relieved by milk and alkali. For instance, Cheli *et al.* (1961b) found that out of 74 patients with radiologically negative dyspepsia, 34 exhibited duodenal inflammatory changes and 40 did not. No explanation was offered for this finding. It is possible that the patients who exhibited inflammatory changes corresponded to our group 3, while the ones with normal mucosa corresponded to our group 2.

The inherent difficulty in the present study was to decide what was normal and what was abnormal duodenal mucosa. Shiner (1956) and Doniach and Shiner (1957) found that the amount of infiltration in the mucosa is variable and thus they were reluctant to assign clinical significance on the basis of such evidence alone. Aronson and Norfleet (1962) noted such a great variability in duodenal mucosa histology that they accepted only very severe changes as evidence of duodenitis. Consequently, with the exception of a few cases, they considered the duodenal mucosa as being normal, even in patients with proven duodenal ulcer. The present study was also subject to this difficulty of interpretation. It is for this reason that at the outset of the study no attempt was made to establish criteria for differentiating normal from abnormal mucosa. Instead, only

after the entire series was collected were the biopsies graded. Arbitrary grades from 0 to 4 were set up without a preconceived idea of what represented normal or abnormal. These gradings therefore are not a measure of normalcy or duodenitis but a relative comparison of one mucosal biopsy with another. Only after the gradings had been completed were they correlated with the pre-established clinical groups. The clinical pathological correlation suggests that the normal variation is what was graded from 0 to 2 and the borderline between normal and diseased lay somewhere between grades 2 and 3. The fact that the biopsies graded 3 or more were found only in patients in groups 3 and 4 suggests that these grades represent significant pathology, *i.e.*, duodenitis.

Another difficulty in this study was the differentiation between the clinical groups. Only by careful history taking could the pain pattern be established in some of the cases of radiologically negative dyspepsia. To be certain of dealing with distinct groups, many patients seen by us were not biopsied or studied since it was not clear into which group to classify them. For instance patients who had the vaguest suggestion of a hunger pain character to their otherwise atypical symptoms were not taken into the study. Similarly patients whose 'atypical' symptoms had ever been relieved by milk or alkali were not investigated since it was impossible to classify them into either group 2 or 3. This explains the small size of group 2. Patients who complained of ulcer pain but in whom radiographs did not exclude a duodenal ulcer with certainty because of an irritable cap, enlarged folds, or unclear duodenal mucosal relief in the absence of an ulcer crater, were also excluded *a priori* since it was impossible to determine whether they belonged to group 3 or 4.

From a physiopathological point of view, the gastric secretory function and duodenal histology in the patients in both group 1 (control) and group 2 (atypical symptoms) would appear normal. Group 4 (proven duodenal ulcer) showed both raised gastric secretions and abnormal duodenal histology. Group 3 (duodenal ulcer symptoms but negative radiological findings) had abnormal duodenal histology but normal gastric secretory response. They thus differ from the first two groups in relation to symptoms and duodenal histology. They differ from the duodenal ulcer group in relation to their gastric secretory response. Although an occasional duodenal ulcer cannot be demonstrated radiologically we do not feel that the patients included in our group 3 could be 'missed ulcers'. They had normal secretory response and only patients with a perfectly normal duodenal radiograph were admitted to the study. Furthermore most of these had more than one barium meal. The findings therefore suggest that this group may represent a clinico-pathological entity 'chronic duodenitis' distinct from either duodenal ulcer or 'functional dyspepsia'.

There is of course the possibility that the patients in group 3 may eventually develop a duodenal ulcer, or, in other words, that duodenitis represents the early stage in duodenal ulcer formation. Ostrow and Resnick (1959), using radiological criteria different from those of the present study for duodenitis have suggested this possibility. Only follow-up of these patients will solve this problem.

The present findings are at variance with the commonly held view that the inflammation and ulcer in the duodenum both result from increased acid secretion. There is no reason why inflammation could not be caused by increased secretion in one group (duodenal ulcer) and by non-specific causes, such as 'decreased mucosal resistance', in others. The results also suggest that gnawing epigastric pain, relieved by food, is not due to hyperacidity, since the patients in group 3 exhibit this symptom complex without having increased acid secretion. It is possible that the inflammation found in both groups 3 and 4 renders the duodenum hypersensitive to acid and other painful stimuli. A further possibility is that the duodenal inflammation is the primary event. In some fashion this could interfere with the gastric secretory inhibitory mechanism of the duodenum (Shay, Gershon-Cohen, and Fels, 1942; Sircus, 1958), resulting eventually in hyperacidity and subsequent ulceration.

As previously mentioned, there are great differences of opinion as to whether duodenitis exists as a clinical pathological entity (Shiner, 1956; Doniach and Shiner, 1957; Mahlo, 1960; Cheli *et al.*, 1961a and b; Aronson and Norfleet, 1962; Ostrow and Resnick, 1959; Bockus, 1964; Palmer, 1957). In their respective papers in *Gastroenterology*, Bockus (1964) and Palmer (1957) infer that no such clear-cut entity exists. In part, the confusion arises from a difference in criteria as to what represents duodenitis. Some investigators have used radiological criteria (Ostrow and Resnick, 1959), some have accepted only specific advanced structural changes in the duodenal mucosa as representing duodenitis (Aronson and Norfleet, 1962), while others, although utilizing pathological features similar to those of the present study, did not correlate these with the clinical picture (Mahlo, 1960; Cheli *et al.*, 1961a and b). No previous study has correlated all four parameters: clinical, radiological, secretory, and histological. On the basis of such correlation, it has been found in the present study that there is a group of patients who differ from normals, true functional dyspeptics, and cases of proven duodenal ulcer.

Whether this group should be called 'duodenitis' or whether this is an early stage in the ulcer diathesis is a question of semantics and remains to be proven on follow-up.

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